



Effect of dihydro-artemisinin on the pharmacokinetics of gliclazide in diabetic subjects

Sambo Godwin ISHAKU^{1,2*}, Mojirade Taibat BAKARE-ODUNOLA³, Aminu MUSA¹, Ibrahim Adamu YAKASAI¹, Magaji GARBA¹ and Bulus ADZU⁴

¹World Health Organization, Kaduna State Office, Kaduna, Nigeria.

²Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Nigeria.

³Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Ilorin, Nigeria.

⁴Department of Pharmacology and Toxicology, National Institute for Pharmaceutical Research and Development, Abuja, Nigeria.

* Corresponding author; E-mail: samboishaku@yahoo.com; Tel: +2348033489096.

ABSTRACT

Diabetic patients do have co-occurring diseases like malaria, especially in tropical regions. Hence, polypharmacy is sometimes unavoidable. Gliclazide is widely used in the treatment of non-insulin-dependent type 2 diabetes mellitus, while dihydro-artemisinin (DHA) is one of the most promising medications used in the treatment of malaria on account of its good efficacy and tolerability. The study evaluated the effect of DHA on the pharmacokinetics of gliclazide in diabetic patients. This is a single dose one-way, cross-over study in two periods, with each phase preceded by an overnight fast. Six subjects that passed inclusion criteria participated in the study. The volunteers acted as their control. Phase 1 of the study involved administering a single oral dose of 80 mg of gliclazide after an overnight fast. After a washout period of one week, 80 mg gliclazide and 120 mg DHA were co-administered. Serial blood samples were collected at time intervals throughout 24 h and processed. A validated HPLC method was used to estimate serum gliclazide concentration, while the glucose oxidase peroxidase method was used in the evaluation of blood glucose concentration. The Pharmacokinetic Software - PharmPK was used to generate the pharmacokinetic parameters. GraphPad Prism version 7.01 software for window was used for data analysis. Statistical differences observed in the pharmacokinetic profiles of gliclazide and blood glucose concentration were not significant. Single oral dose of gliclazide and dihydro-artemisinin had good safety and tolerability in diabetic subjects.

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INTRODUCTION

Diabetes mellitus (DM), a group of diseases with a variety of causes due to the disorder of metabolism, is characterized by high blood glucose levels (WHO 2016; CDC, 2017). Over time, this damages nerves and

blood vessels, leading to complications such as heart disease, blindness, stroke, dental diseases, kidney disease, and amputations. DM has other complications, including increased susceptibility to other diseases, loss of mobility with aging, depression, and pregnancy

problems (CDC, 2017). The condition can cause pathophysiological changes in the body that include a reduction in gastric emptying time, albumin glycation, and CYP activity; that affect the pharmacokinetics and pharmacodynamics of drugs (Stachowiak et al., 2019).

Diabetes mellitus is mainly of 2 types: type 1 (insulin-dependent). It is usually first diagnosed in children, teenagers and young adults, and type 2 (non-insulin dependent) often related to old age—gestational diabetes associated with pregnancy. Gliclazide plays a vital role in the treatment of type 2 diabetes mellitus (Yang et al., 2018). It helps improve insulin secretion in the body by blocking K^+ channels in the pancreatic β cells and increasing tissue uptake of glucose (Sandoz Product Monograph, 2018) and inhibition of vascular smooth muscle cell proliferation through the CaMKK β –AMPK pathway (Lee et al., 2018).

Artemisinin Combination Therapies (ACTs) are currently the frontline treatment of uncomplicated /multidrug-resistant *P. falciparum* malaria. They produce rapid and profound reductions/elimination of parasitemia. Dihydro-artemisinin based combinations remain one of the most-likely, on account of its good efficacy and tolerability (Hasugian et al., 2007; Millat-Martinez et al., 2018). Diabetic patients do have comorbidities with malaria infestation, especially in tropical regions. In such malarial endemic areas, the need for polypharmacy for most diabetic patients becomes evident in most patients (Greenblatt et al., 2017) and sometimes unavoidable for such patients, thereby increasing the likelihood of drug-drug interactions. It has been known that polypharmacy is a risk factor in the treatment of diabetes (Austin, 2006), which requires proper care and better quality of drugs (Ribeiro da Silva, 2018). Some studies showed 91.2% of diabetic patients have comorbidities (Geitona et al., 2017); hence, polypharmacy is sometimes unavoidable for such patients (AL-mohamadi and Ibrahim, 2015). The fact is that it is a growing phenomenon (Pinnamraju et al.,

2018) and shared in diabetic patients (AL-mohamadi and Ibrahim, 2015) hence complicating diabetes management (Peron et al., 2015). The study of drug-drug interactions becomes vital to ascertain the safety and efficacy of such drugs (Mandlem et al., 2014).

Several studies have confirmed the influence of diabetes mellitus on the pharmacokinetics of drugs (Stachowiak et al., 2019). Since maintenance of normal blood glucose levels is essential in diabetes monitoring of anti-diabetic drug therapy in the presence of other drugs, the influence of such drugs needs to be evaluated to maintain safety (Kilari et al., 2012). Recently, we started testing common antimalarials on the pharmacokinetics of gliclazide in diabetic subjects to assess their safe and efficacious use. Part 1 of the study was on amodiaquine (Ishaku et al. 2019a), while Part 2 was on artesunate (Ishaku et al., 2019b). In this continuation, the study evaluated the effect of dihydro-artemisinin on the pharmacokinetics of gliclazide in diabetic subjects.

MATERIALS AND METHODS

Subjects and ethical clearance

The diagnosis of diabetes mellitus was established at the medical outpatient department of Barau-Dikko Teaching Hospital in Kaduna, Nigeria. Kaduna State Ministry of Health Ethical Committee approved this study (approval number MOH/ADM/744/T/17, dated 28 January 2010) per the National Code of Health Research Ethics (2006) under Federal Ministry of Health, Nigeria; and also, with the Helsinki declaration (1964) and its later amendments or comparable ethical standards. The study was carried between October 2011 and December 2011 at Barau-Dikko Teaching Hospital (formerly, Barau-Dikko Specialist Hospital), Kaduna. Written informed consent was obtained, documented, and archived.

Inclusion/exclusion criteria

Before the start of the study, a structured questionnaire was filled for each volunteer, which included medical history,

clinical and laboratory data, and prior hospital admissions. Volunteers included for the study are freshly diagnosed patients who were on lifestyle modification, willingness to fill an informed consent form, non-smokers, which are not alcohol drinkers, and are willing to abstain from heavy exercise during the study period. They were not on other medications during the study, and have agreed to refrain from caffeine. The volunteer also met a Body Mass Index (BMI) of less than 30 kg/m². Subjects who are Pregnant and those currently undergoing any medication or planned treatment during the study period were excluded from the studies.

Study design and blood sampling

The protocol adopted was a cross-over, one-way single-dose study in two phases. Each phase followed an overnight fast. The subjects act as their control. The first phase of the study involved the administration of a single oral dose of 80 mg of gliclazide after an overnight fast. After a washout period of one week, 80 mg gliclazide and 120 mg DHA were concomitantly administered. Blood samples (5 ml) were collected serially at intervals ranging from 0, 0.5, 1, 2, 4, 6, 8, 12, 16, and 24 h during each phase into an EDTA vacutainer.

Blood sample processing

After collection, blood samples were centrifuged at 2000 rpm, and plasma kept frozen in a freezer maintained at -20 °C after which, it was analyzed. For gliclazide to be extracted from the plasma, the frozen plasma was thawed and to 1.0 ml of plasma was added 0.1 mL of glipizide (internal standard, 20 µg/ml), 0.2 ml of 0.4 mol/l of HCl, with 5.0 ml of benzene- isopropanol (98:2, v/v), and this was vortex-mixed for 2 minutes. This was followed by centrifugation of the mixed samples at 2000 rpm for 5 min, after which the upper layer (4.0 ml) was placed into another tube and was dried in a hot air oven (Mettler 854 Schwalbach-Germany) at 40 °C. Methanol (0.15 ml) was used to resolve the dried residue, and 20 µl of the solution was injected into the liquid chromatography.

Determination of plasma gliclazide concentration

A validated HPLC method (Yang et al. 2004) was used in the estimation of serum gliclazide concentration using an HPLC instrument (Shimadzu® chromatograph-LC-10 series, Japan) as earlier described (Ishaku et al. 2019a). The system used (Shimadzu Corporation, Kyoto Japan) consists of Ultra-Fast LC-20AB prominence with the following accessories: UV-diode array detector; SPD-M20ASIL-20AC auto-sampler; CTO-20AC column oven; DGU-20A3 degasser; 5µm VP-ODS C₁₈ and dimensions (4.6 x 150 mm); CBM-20Alite system controller and Windows software (LCsolution). The chromatographic set-up was made up of the mobile phase with solvent A, being water (pH 2.8) 51% and solvent B being acetonitrile 49%; in the isocratic mode. The HPLC flow rate was 1 ml/min; injection volume of 20 µl, a detection wavelength, UV 229 nm, and a Column oven temperature of 40 °C. The internal standard used was glipizide, and the total run time was 7.5 min.

Determination of glucose concentration

Glucose oxidase peroxidase method (Trinder, 1969) was used to determine plasma glucose concentration was measured throughout 24 h at 9-time point's interval. 10 µl of the plasma sample (A_{sample}) or standard (A_{standard}) was transferred into a microcentrifuge tube (1.5 ml) which contained 1000 µl of glucose reagent (Randox), and this was well mixed and incubated for at 20±5 °C for 10 min. The mixture, which became slightly pink, was then transferred to a 1cm path length cuvette, and the absorbance of the standard and sample was measured at λ 500 nm against the 1000 µl reagent blank within 30 min. The equation below (Glucose Concentration (mmol/L) = $\frac{A(\text{sample})}{A(\text{standard})} \times 5.5$) was used to determine plasma glucose concentration during the two phases of the study and were compared.

Pharmacokinetic analysis

The Non-compartmental method was used for Pharmacokinetic analysis using the Pharmacokinetic Software - PharmPK software (Joel et al. 2012). The following Pharmacokinetic parameters were generated: Maximum plasma concentration (C_{max}), Time to maximum plasma concentration (T_{max}), Total body clearance (Cl), Volume of distribution (VD), Area under the curve from zero hours to last measurable concentration (AUC_{0-t}), Area under the curve (from zero hours to infinity ($AUC_{0-\infty}$), Area under the Moment curve from zero hours to last measurable concentration (AUMC 0-t), Area under the Moment curve from zero hours to infinity ($AUMC_{0-\infty}$), Elimination half-life ($t_{1/2eli}$), Elimination rate constant (K_{eli}). The method of residual was used to generate Absorption half-life ($t_{1/2abs}$), Absorption rate constant (K_{abs}) using Microsoft excel. Total body clearance (Cl), the volume of distribution (VD), and Mean residence time (MRT).

Data analysis

Data were expressed as mean \pm SEM. GraphPad Prism Version 7.01 software for Windows (San Diego California, USA) was used for data analysis using Student's T-test with $p < 0.05$ considered significant.

RESULTS

Subjects

Six freshly diagnosed diabetic subjects (two males and four females) on dietary and lifestyle modification met the inclusion criteria. Their mean age (years) was 53.8 ± 0.962 , and the mean Body Mass Index (BMI) of 24.78 ± 0.353 . All subjects completed the treatment periods and were included in the pharmacokinetic analysis.

Plasma gliclazide concentration

Table 1 showed the mean pharmacokinetic parameters generated after a single oral dose of 80 mg of gliclazide alone and when used concomitantly with 120 mg of DHA. Changes in the C_{max} (95% CI=-1.218 to 2.684 $\mu\text{g/ml}$, $R^2=0.1572$), T_{max} (95% CI=-

2.794 to 5.461 h, $R^2=0.1212$), $T_{1/2abs}$ (95% CI=-1.261 to 1.228 h, $R^2=0.0002318$), K_{abs} (95% CI=-0.8243 to 0.5952 h^{-1} , $R^2=0.03327$) AUC_{0-t} (95% CI=-10.24 to 20.97 $\mu\text{g.h/ml}$, $R^2=0.1351$) $AUC_{0-\infty}$ (95% CI=-9.027 to 22.46 $\mu\text{g.h/ml}$, $R^2=0.194$) $AUMC_{0-t}$ (95% CI=-63.74 to 205.1 $\mu\text{g.h}^2/\text{ml}$, $R^2=0.2676$) were observed. Although there is a difference in the values between the control and co-administer phase, all the pharmacokinetic parameters generated were not significantly altered ($p > 0.05$) clearly denoting a lack of significant pharmacokinetic interactions between gliclazide and dihydroartemisinin (Figure 1).

Changes in the MRT (95% CI=-22.21 to 14.49 h, $R^2=0.05523$), Cl (95% CI=-1786 to 175.8 ml/h, $R^2=0.471$) K_{eli} (95% CI=-0.03678 to 0.06555 /h, $R^2=0.09457$) $T_{1/2eli}$ (95% CI=-3.902 to 2.701 h, $R^2=0.04187$) were not statistically significant ($p > 0.05$) for these parameters. The data shows that the metabolism and elimination of Gliclazide were not significantly affected by the presence of DHA.

The concentration versus time profile of gliclazide when administered alone, and in the presence of DHA, is shown in Figure 1. For the control, there was a gradual increase in mean gliclazide concentration from zero h to a maximum at 4.33 h then a gradual decrease at the C_{max} ($\mu\text{g/ml}$), with a range of 1.4085-5.0959 $\mu\text{g/ml}$; whereas for the co-administration of gliclazide with DHA, there was a C_{max} ($\mu\text{g/ml}$) range of 2.0196 -4.9836.

Glucose concentrations

The mean plasma glucose concentration is given in Table 2. There was a minimal increase in plasma glucose concentration between 0.5 h – 8 h ranging from between 3 and 12 %, while a decrease in blood glucose concentration was observed between 12 and 24 h ranging from between 8 and 20%. These observed changes were not significant ($p > 0.05$). There was a concordance between the maximal plasma concentration of gliclazide and the maximum decrease in plasma glucose concentration (Figure 2).

Table 1: Mean Pharmacokinetic parameters of Gliclazide (n=6).

	Control (Gliclazide alone)		Gliclazide+Dihydro-Artemisinin		The T-Test (paired value)	
	Mean	SEM(±)	Mean	SEM(±)	(P-Value)	
C _{max} (µg/ml)	2.989	0.201	3.722	0.168	p>0.05	(p=0.3785)
T _{max} (h)	4.333	0.234	5.667	0.272	p>0.05	(p=0.4441)
K _{eli} (h ⁻¹)	0.099	0.030	0.113	0.033	p>0.05	(p=0.5023)
T _{1/2 eli} (h)	7.633	0.257	7.033	0.297	p>0.05	(p=0.6598)
AUC _{0-t} (µg.h/ml)	31.085	0.656	36.451	0.495	p>0.05	(p=0.4173)
AUC _{0-inf} (µg.h/ml)	36.059	0.805	42.778	0.591	p>0.05	(p=0.3227)
AUMC _{0-t} (µg.h ² /ml)	261.183	2.019	331.867	1.775	p>0.05	(p=0.2344)
AUMC _{0-inf} (µg.h ² /ml)	441.871	2.989	506.731	3.355	p>0.05	(p=0.7092)
MRT (h)	14.698	0.646	10.839	0.456	p>0.05	(p=0.6120)
Cl (mlh ⁻¹)	2806.956	6.969	2001.722	4.686	p>0.05	(p=0.0886)
VD (ml)	28993.417	22.289	19561.494	17.986	p>0.05	(p=0.2572)
T _{1/2 abs} (h)	1.704	0.201	1.687	0.212	p>0.05	(p=0.9742)
K _{abs} (h ⁻¹)	0.663	0.157	0.548	0.155	p>0.05	(p=0.6955)

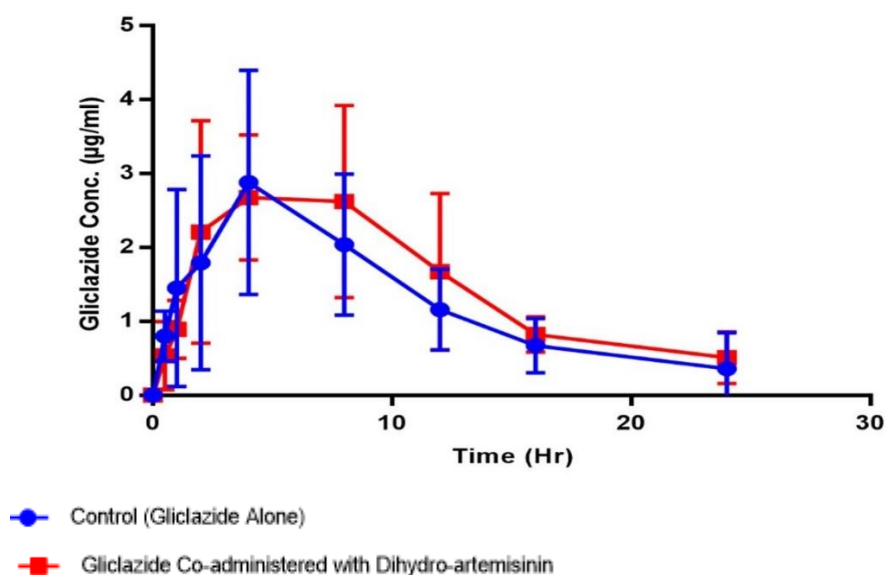


Figure 1: Mean plasma gliclazide concentration-time profile.

Table 2: Blood glucose concentration (mmol/l).

Time (h)	Control (Gliclazide alone)		Gliclazide+DHA		T-Test	
	Mean	SEM(\pm)	Mean 2	SEM (\pm)		
0	8.201	0.185	7.914	0.245	$p>0.05$	($p=0.8039$)
0.5	7.683	0.250	7.938	0.281	$p>0.05$	($p=0.8773$)
1	7.117	0.251	7.832	0.253	$p>0.05$	($p=0.6449$)
2	6.612	0.216	7.388	0.244	$p>0.05$	($p=0.5397$)
4	5.797	0.201	6.016	0.211	$p>0.05$	($p=0.8332$)
8	5.897	0.280	6.045	0.305	$p>0.05$	($p=0.9519$)
12	8.918	0.237	7.134	0.185	$p>0.05$	($p=0.1230$)
16	10.249	0.197	8.985	0.274	$p>0.05$	($p=0.4140$)
24	10.088	0.289	9.316	0.254	$p>0.05$	($p=0.6725$)

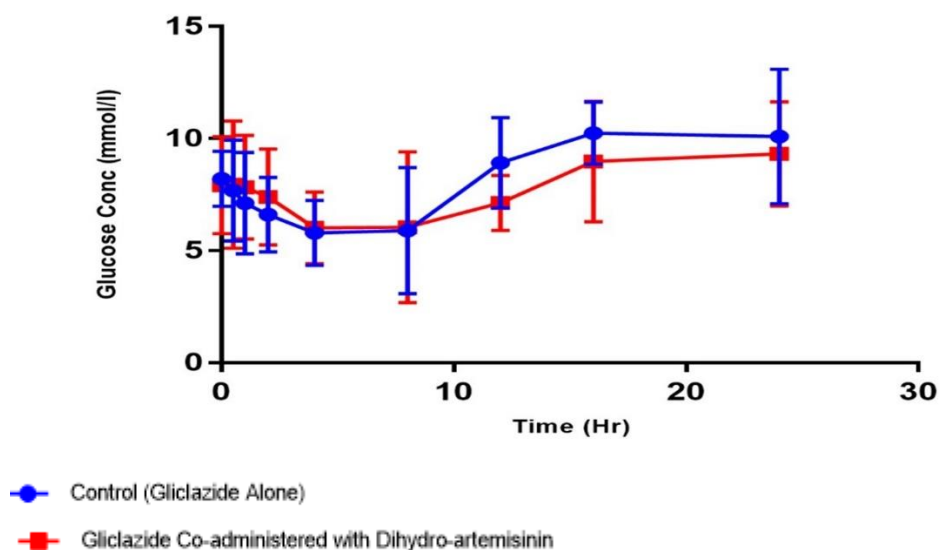


Figure 2: Mean plasma glucose concentration-time profile.

DISCUSSION

The influence of diabetes on drug metabolism in polypharmacy has not been thoroughly investigated even though it is a growing phenomenon (Pinnamraju et al., 2018) and shared in diabetic patients (AL-mohamadi et al., 2015). This study's objective was to evaluate 120 mg of DHA with a co-administered with 80 mg gliclazide in diabetic subjects. Freshly diagnosed diabetes subjects which were not yet placed on treatment but were on diet and exercise participated in the study; this is to preclude the need for simultaneous drug intake during the course of the study. For this work, the differences in pharmacokinetic parameters of gliclazide and plasma glucose level for both phases of the study were studied. Healthy volunteers as a study group were not used in the study for comparison purposes; hence the effect of disease state on the pharmacokinetics of gliclazide might be a potential source of bias.

The pharmacokinetic and pharmacodynamic interactions of gliclazide with several drugs have been reported. Drugs like rifampicin affect the disposition of gliclazide in humans, with both pharmacokinetics and pharmacodynamics implications (Park et al., 2003). Other drugs for which there are significant interactions with gliclazide are efavirenz (AL-mohamadi et al., 2015), St. John's wort (Xu et al., 2008), Ayuslim herbal drug (Mandlem et al., 2014) and capsaicin (Lagisetty et al., 2018). However, some studies showed a lack of interactions with gliclazide (Delrat et al., 2002), among others. In light of this information, it becomes essential to ascertain the pharmacokinetic interactions of Gliclazide with drugs that are commonly co-administered like the antimalarials.

As shown in the result, all the pharmacokinetic parameters generated were not significantly altered ($p > 0.05$), clearly denoting a lack of significant pharmacokinetic interactions between gliclazide and DHA. Changes in clearance and elimination half-life were not statistically significant ($p > 0.05$). This data shows that the metabolism and

elimination of Gliclazide were not significantly affected by the presence of dihydro-artemisinin. A change in the clearance, MRT and elimination half-life has implications for the duration of action of the drug in the body (Triplitt, 2006). A mean low volume of distribution of 28 L was generated for gliclazide when administered alone, consistent with the literature. Drugs, having this low volume of distribution as with gliclazide, which is reported to have a protein binding up to 84-99% (Campbell et al., 1991), is highly protein-bound. A drug interaction that affects protein binding affects the distribution of the drug in the system. Displacement from the binding site may lead to increase concentration and or increase in therapeutic effect or toxicity depending on the therapeutic index of the drug (Triplitt, 2006). One drug can displace another from the binding sites on the plasma proteins if the binding is more durable. Changes observed in the volume of distribution were not significant ($p > 0.05$). However, the data showed that the displacement of gliclazide from protein binding sites by dihydro-artemisinin could not be concluded. No significant distribution interactions are pertinent for oral medications commonly used for diabetes (Benet and Hoener, 2002).

To complement the pharmacokinetic data, the pharmacodynamics of gliclazide was assessed in terms of glucose concentration. Plasma glucose concentration was measured throughout 24 h at nine interval time points. In the plasma glucose concentration for all time points between the two phases of the study were compared. There was a minimal increase in plasma glucose concentration between 3 and 12% at 0.5 h to 8 h, and a 20% decrease in blood glucose concentration observed between 12 and 24 h. These changes were, however, not significant ($p > 0.05$), and there was concordance between maximal plasma concentration of gliclazide and the maximum decrease in plasma glucose concentration (Figure 2). Thus, pharmacodynamic findings were in agreement with pharmacokinetic results. Blood glucose concentration was seen to increase gradually after the maximum

reduction. This might indicate the presence of fasting hyperglycemia that could lead to the worsening of diabetes state in the studied patients. It is possible that the subjects have had diabetes for a long time before diagnosis.

Conclusion

These findings showed that administering a single oral dose of gliclazide and dihydro-artemisinin did not alter gliclazide's disposition in diabetic subjects. A study after a multiple-dose administration of these drugs is suggested to see if similar effects can be observed.

COMPETING INTERESTS

The authors have no relevant conflict of interest. For this study and publication, no funding was received

AUTHORS CONTRIBUTIONS

SGI, MTB, AM, IAY, MG, designed the study; SGI collected samples; SGI and BA performed the experiment, analyzed result and wrote the draft of the manuscript. All authors read and made input to the final draft. The authors declare that all data were generated in-house and that no paper mill was used.

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ETHICAL CONSIDERATION

The procedures performed in studies were as per the National Code of Health Research Ethics (2006), Federal Ministry of Health, Nigeria), and with the Declaration of Helsinki and good clinical practice guidelines. The health ethics committee of Kaduna State Ministry of Health (approval number MOH/ADM/744/T/17, dated 28 January 2010).

All subjects provided written informed consent before participation.

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